Cell, Vol. 100, 1–11, January 7, 2000, Copyright ©2000 by Cell Press

Evolution: Bringing Molecules into the Fold

Review

Simon Conway Morris
Department of Earth Sciences
University of Cambridge
Cambridge CB2 3EQ
United Kingdom

Introduction

When discussing organic evolution the only point of agreement seems to be: "It happened." Thereafter, there is little consensus, which at first sight must seem rather odd. Towering majestically over the citadel is the figure of Darwin. In squares and piazzas the other heroes of evolution stand in marmoreal splendor: Bateson, Morgan, Dobzhansky, Simpson, and, just completed, Lewis and Nüsslein-Vollhard. These are the grand architects of the evolutionary synthesis, and together they provide a narrative for everything from the study of variation and the genetic structure of populations to the remarkable discoveries of homeotic genes. Given, therefore, this history and the most recent and spectacular advances in molecular biology, it may seem curmudgeonly, if not perverse, to even hint that our understanding of evolutionary processes and mechanisms is incomplete. Yet, this review has exactly that intention.

There is a paradox in as much as sensible advances are usually only possible under a severely reductionist program, whereas questions basic to our understanding of evolution demand an encyclopedic knowledge of the science combined with an unprecedented skill in distillation and synthesis. Of these questions, perhaps the most fundamental is to explain the immense diversity of life despite its deep and pervasively similar molecular architecture. One answer is to invoke the presence of new genes, and then introduce them to a constantly shifting ecological and physical environment. In itself, however, this sort of answer is hardly sufficient. Here I wish to tackle four major questions that inevitably emphasize present ignorance but also, hopefully, indicate future possibilities: (1) What is the connection between phenotype and genotype? (2) Evolution has a temporal framework, but molecular "clocks" now plot a history of life seriously at odds with the fossil record. Which is correct? (3) Do data from molecular biology offer insights into mechanisms of macroevolution? (4) Constructing phylogenies is central to the evolutionary enterprise, yet rival schemes are often strongly contradictory. Can we really recover the true history of life?

Phenotype and Genotype

The fact that the arm that brandishes the newspaper, the eye that scans the room, the heart that pumps the blood, and even the entire orientation of the body all find corresponding genomic counterparts (e.g., *Pax-6*, *tinman*, etc.) in the fly buzzing around the room is almost too well known to require further emphasis. And such deep and pervasive similarities amongst the metazoans seem to be the rule. Consider, for example, the sponges, which by general consent are the most primitive living metazoans. Nevertheless, their biochemistry includes elements that seem to foreshadow the immune system of vertebrates (e.g., Schäcke et al., 1994). Sponges do not have nerve cells, but paradoxically they possess neuronal-like receptors (Perovic et al., 1999). Moreover, in one group of sponges (the hexactinellids), electrical impulses have been detected (Leys et al., 1999). Even though their unusual syncitium might be peculiarly conducive to such propagation, some evidence suggests hexactinellids are the most primitive of the sponges (Müller et al., 1998). With such features, sponges seem to be almost "animals in waiting": everything is in place but nothing happens. This, however, is a distorted view. First, many of the basic building blocks and processes found in the metazoans are very widespread among eukaryotes and must have originated much earlier than the first animals (e.g., Chiu et al., 1999) (Figure 1). Second, sponges are well adapted, abundant, and diverse. They are highly organized, capable of coordinated responses, and despite the relative simplicity of their bodyplan, some sponges demonstrate a radical reorganization concomitant with a shift to carnivory (Vacelet and Boury-Esnault, 1995).

A related problem concerns what might be called molecular inherency, which is when a gene known to be of major importance in organogenesis in a higher animal also occurs in a more primitive group. There are many such examples. In the sponges, equivalents to a number of the *Pax* genes, specifically *Pax 2/5/8*, exist (Hoshiyama et al., 1998). Similarly the gene family *otx*, known to be of key importance in the formation of head and brain in arthropods and vertebrates (see Finkelstein and Boncinelli, 1994), also occurs in the cnidarians (Figure 2) (or at least *Hydra*; Smith et al., 1999). These authors showed that the cnidarian *otx* seems to play no part in the formation of the *Hydra* "head," but it is important in cell movements. On the other hand, the gene *empty spiracles* (*ems*), a key element in the development of the bilaterian head, is expressed in an area of a hydrozoan zooid that might be equated with the head (Mokady et al., 1998).

At a more advanced level, the amphioxus (the most primitive living chordate, widely regarded as a sort of pre-fish) also provides some good examples of such inherency. Molecular data strongly support the notion that this animal is the most primitive living chordate, notably in terms of its possession of a single *Hox* cluster. Continuing genomic investigations (e.g., Williams and Holland, 1998) and careful histological studies of such features as the eye (e.g., Lacalli, 1996), the nervous system (Lacalli et al., 1999), and the organ known as the endostyle (primitively a ciliated gutter on the floor of the pharynx that ultimately gives rise to the thyroid) (Holland and Holland, 1999) again reveal a "vertebrate in waiting." In this case, however, the evidence for gene duplications, and presumably new regulatory pathways, could allow a closer tracking between genomic innovation and the emergence of the vertebrate bodyplan. Even so, it is necessary to remain cautious about making

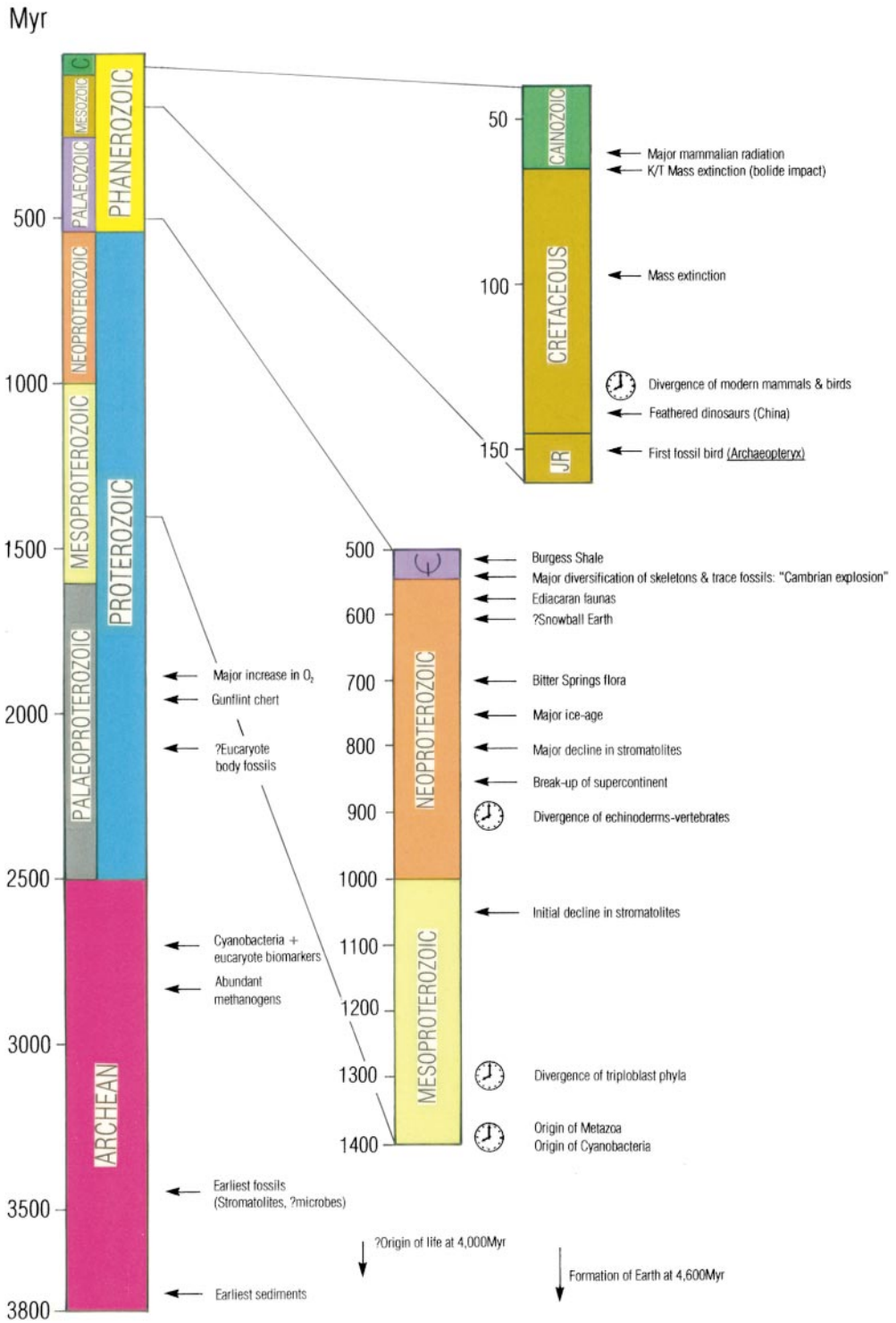

Figure 1. Geologic Time and Stratigraphic Record with Reference to Some Key Evolutionary Events

The left-hand column depicts geological time from ca. 3,800 million years (Myr) ago, which marks the onset of an effective sedimentary record with clear evidence for water-borne processes, implying the presence of at least seas, if not oceans. Slightly older rocks are also known, but these have been greatly altered by heat and pressure. Accordingly, practically nothing is known of the first Eon of Earth history, the Hadean, that spans the interval from the formation of the Earth (ca. 4,600 Myr) to the first record of surface processes (ca. 3,800 Myr). The remainder of Earth history is divided into three more Eons, the Archaean, Proterozoic, and Phanerozoic. The latter two are further subdivided, and the Phanerozoic is defined by a series of rather short intervals e.g., Cambrian (Є), Cretaceous (K), on the basis of a continuous and changing fossil record. The two columns to the right show selected enlargements of two critical intervals of Earth history (40–150 Myr and 500–1400 Myr), referred to in the text, with key events indicated, as well as divergence times as estimated on the basis of molecular clocks.

direct correlations between gene duplication events and evolutionary radiations. For example, Ono et al. (1999) infer an explosive gene duplication in metazoan protein-tyrosine phosphatases that must have substantially predated the Cambrian explosion. Although this event is conceivably connected to the evolution of multicellularity, apparently it did not in itself trigger an adaptive radiation.

These examples of genomic inherency pose, in turn, questions of genetic cooption, in which an existing gene (and its product) is recruited to a new function. The crystallins are a textbook example (Wistow, 1993). These proteins evolved in the context of heat shock and other stress resistance, which, together with their small size and ability to pack into regular arrays, allows their cooption to build transparent and stable eye lenses. Cooption is widely acknowledged to be pervasive, although determining the primitive function as opposed to derived acquisitions of particular genes is not always as straightforward as for crystallins. Take, for example, *Pax-6*. This is most famously linked to the formation of eyes in many, and perhaps all, metazoans (e.g., arthropods, molluscs, vertebrates, and probably cubozoan cnidarians). Yet *Pax-6* is also involved in the development of the nose, central nervous system, and even the pancreas. Usually, and somewhat vaguely, its original function is placed in the context of the early patterning of the anterior nervous system and associated sensory features. Can we specify an original function more exactly, as well as phylogenetically tracking its recruitment to new purposes? At present, apparently not. Progress is, however, surely imminent. Peterson et al. (1999), for example, offer a good example in the case of *Brachyury*, which is best known for its role in the chordates with the development of the notochord. But Peterson et al. suggest that primitively *Brachyury* was involved in expression of the posterior gut, a function it retains in flies and presumably other protostomes.

Cooption is, therefore, commonplace (e.g., Finkelstein and Boncinelli, 1994; Holland and Holland, 1999), perhaps ubiquitous, and just what we would expect in organic evolution. How, why, and when cooption occurs is, however, only now beginning to be explored (e.g., Wray, 1999). And there is potentially a much more interesting problem that questions whether genetic similarity, however striking, can be equated in any simple fashion with a shared ancestry. Nagy (1998, pp. 818–819), for example, asks: "Should vertebrate and insect limbs be considered homologous because they are patterned by similar gene networks? Or is the similarity an example of molecular convergence, representing not an extreme conservation of limb construction throughout metazoa, but merely a consequence of a limited number of molecular tools an organism has available to change its form?" As Nagy goes on to indicate with respect to limb development, the conditions in the intermediate clades that separate vertebrates from insects (Figure 2) simply are not yet known. In a similar vein, Williams and Holland (1998) caution against what may be an oversimplified view of the role of *otx* in vertebrate evolution. As they note, comparisons with development in some insects show certain differences in *otx* expression, and while conservation of function seems most plausible, "convergent evolution cannot be ruled out by current molecular evidence" (p. 606).

Indeed, behind the current triumphalism there is a sense of unease. Consider, for example, the now classic story of a dorso-ventral inversion between the protostomes and deuterostomes. These are the two major groups of advanced metazoans, and their names derive respectively from the fate of the embryological blastapore. In protostomes, such as annelids and arthropods, it goes to form the mouth, whereas in the deuterostomes (e.g., chordate, echinoderm) the mouth is a secondary development. The discovery that in terms of molecular expression, the dorsal side of a deuterostome is equivalent to the ventral side of the protostome (e.g., De Robertis and Sasai, 1996; see also Arendt and Nübler-Jung, 1999) created a sensation, even as it confirmed the apparently wild conjectures of the early nineteenth century biologist Geoffroy Saint-Hilaire, who defied received wisdom when he pointed out a lobster oriented upside down could potentially be transformed into a vertebrate. Now Davidson and Ruvkun (1999) gently question received orthodoxy by reminding us that cooption of genes might be analogous to plugging of particular computer "chips" into a new program. And a further hint of this possibility is apparent in the rather astonishing discovery (Wu and Lengyel, 1998) that the molecular architecture involved in the gastrulation of protostome and deuterostome larvae, which in classic embryology define the mouth and anus respectively, is the same. Perhaps the processes of gastrulation per se require a particular gene network, and we should be correspondingly cautious in homologizing mouth and anus. Only when a particular gene network is mapped onto a phylogeny (the reliability of which will need to be established independently) can we properly explore homologies (see also Holland and Holland, 1999).

The connection, or lack thereof, between phenotype and genotype has many other interesting ramifications. It has long been known, for example, that some groups, e.g., sea urchins, may have wildly different ontogenetic trajectories, with fertilized eggs developing into very different types of embryo that subsequently converge on similar forms of adult. Gene networks will probably be altered, perhaps radically. Detailed genomic information on ontogenetic pathways is still rather limited, but the work on the development of the vulva in nematodes indicates that despite a near-identical end product, there is considerable genetic lability in cell fates and dispositions (e.g., Eizinger and Sommer, 1997; see also Eizinger et al., 1999). Multiple genomic pathways in ontogeny are probably the rule, but in our present state of knowledge, this seems rather surprising given that once a particular pathway is established, the advantages of altering it, when the end-product remains unchanged, are obscure.

One way of constraining part of this problem might be to look at examples of massive anatomical simplification, anthropomorphically encapsulated in the notion of degeneracy. Here, in principle, there could be a wholesale reduction of genomic needs and requirements. One example might occur in the nematodes. In contrast to the related phyla, e.g., arthropods, which together define the Ecdysozoa (see Figure 2), this group appears

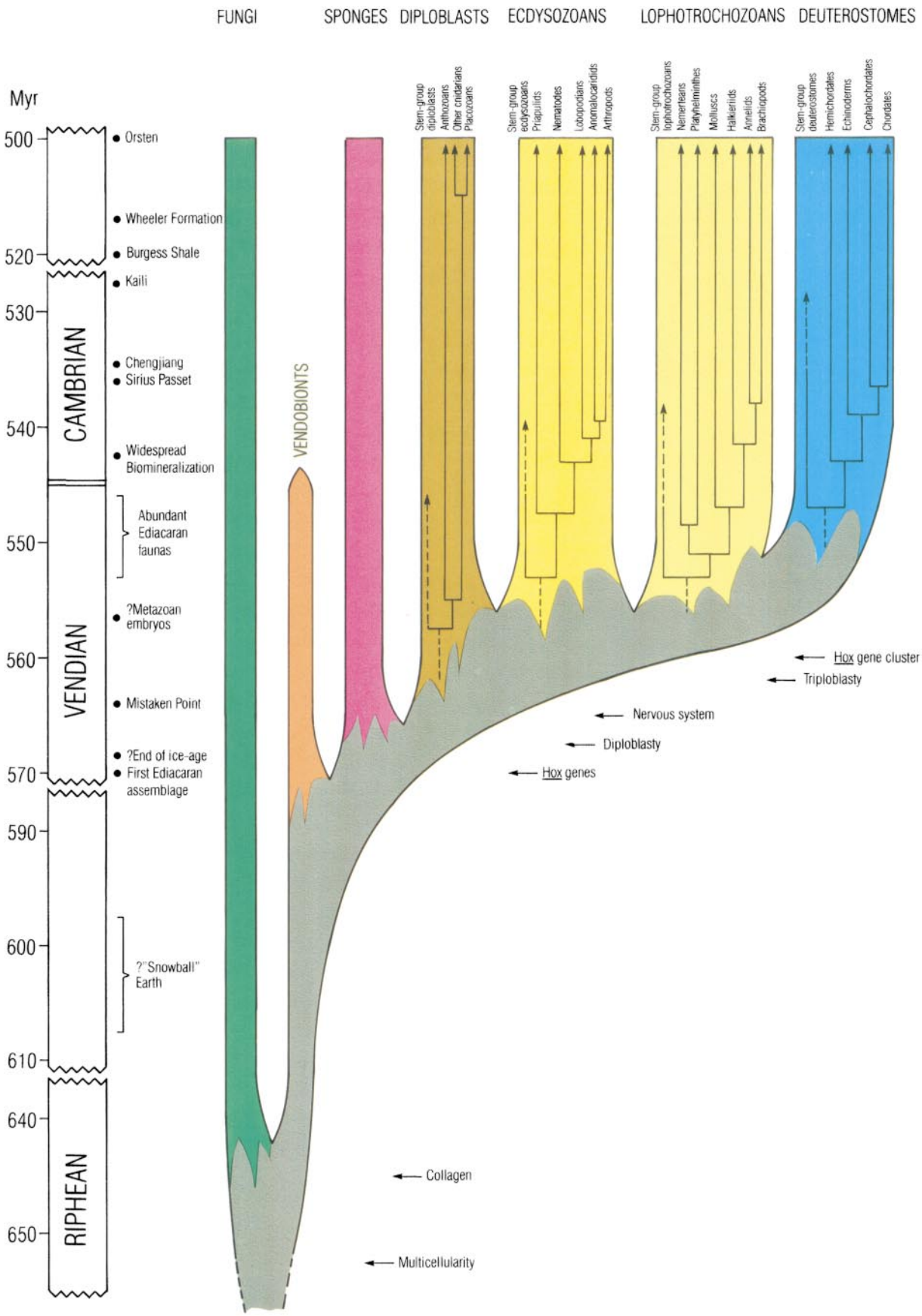

Figure 2. Time-Scale and Main Branches of Metazoan Phylogeny

to have a reduced complement of *Hox* genes (de Rosa et al., 1999). Nematodes were once regarded as a peculiar offshoot of metazoans, placed in a phylogenetic "dustbin" referred to as the aschelminthes. This group, the concept of which once commanded considerable currency, included a number of otherwise disparate phyla whose true position in metazoan phylogeny is only now emerging. Had the simplified *Hox* complement of the nematodes been discovered earlier, it would probably have been interpreted as an indication of primitiveness. The evidence for simplification in other groups is similarly important because of the prior and widespread assumption that such groups were basal to more advanced clades. Significant examples, that are not household names but have been central to discussions of metazoan evolution, include the platyhelminthes (e.g., Balavoine, 1998; but with the possible exception of the acoels (Ruiz-Trillo et al., 1999; see also Reuter et al., 1998)), the placozoans (Schierwater and Kuhn, 1998), the mesozoans (e.g., Hanelt et al., 1996; Kobayashi et al., 1999), and the xenoturbellids (e.g., Noren and Jondelius, 1997) (see also Figure 2). In each example, the primitiveness of the group has now been questioned, and in the case of yet another group, the myxozoans (e.g., Siddall et al., 1995), molecular data have even led to their rescue from the Protista. Such redeployments not only have implications for our understanding of what, for example, might constitute either a basal metazoan (in the case of placozoans; see Collins, 1998) or primitive triploblast (as was previously argued for platyhelminthes and xenoturbellids), but they also remind us of the inadvisability of constructing scenarios concerning, for instance, the evolution of the brain (e.g., Umesono et al., 1999; and see also Reuter et al., 1998), on the supposedly primitive status of certain groups.

To conclude: connecting genotype to phenotype is not always straightforward. Despite classic cases of conservation, mapping on to a properly constructed diagram of evolutionary relationships and descent—that is, a phylogeny—will probably reveal a more complex picture, possibly even involving convergences. Primitive organisms, such as sponges, or even protists for that matter, appear to be genomically elaborate, whereas some derived and simplified types can show a corresponding genomic impoverishment. In addition, genetic pathways are likely to be various and complex, and while cooption is the rule, we understand neither why particular genes are chosen nor the basis of this genetic lability. In brief, nothing is simple.

Do We Need to Rescale the History of Life?

While no paleontologist would claim the fossil record is perfect, in general it appears to be good enough to give coherent historical insights (Donovan and Paul, 1998). This, however, has been vigorously disputed by exponents of the molecular "clock." The basis of this method depends not only on the reasonable notion that proximity of evolutionary relationships will be revealed in similarities of amino acid or nucleotide sequences (and vice versa for distantly related organisms), but more importantly that the rate of substitution occurs at a sufficiently regular rate to act as a chronometer. The point at issue is that the fossil record and molecular "clocks" consistently show major differences in the estimated times of divergence. Typically, but not invariably, the clocks point to a protracted and (by definition) cryptic history that significantly predates the appearance of the first fossils (see Conway Morris, 1998a). Should molecular clocks be taken as a serious guide to the evolutionary timetable? Opinion is strongly polarized. Some workers (e.g., Cooper and Penny, 1997; Bromham et al., 1998) exhibit serene confidence, whereas others have difficulty hiding their exasperation at what they see as the credulity of the opposing camp (e.g., Cavalier-Smith et al., 1996; Lynch, 1999; Valentine et al., 1999). Such suspicions seem to be justified. Not only do different molecules and lineages (e.g., Britten, 1986) show wide variations in substitution rates, but it is also doubtful whether rates are constant over protracted intervals. Kupfermann et al. (1999; see also Britten, 1986), for example, present intriguing evidence for a pronounced shift in substitution rates in the primates with the clock "ticking" much faster prior to ca. 50 Myr. It is also questionable whether extrapolation of clock-like behavior into the

The left-hand column provides stratigraphic nomenclature and estimated radiometric dates for the Neoproterozoic and Cambrian, as well as some key events, e.g., global glaciation or "Snowball" Earth, and exceptional faunas, e.g., Burgess Shale. To the right is an outline phylogeny depicting our current understanding of metazoan interrelationships, possible times of origination (which note are strongly at variance with evidence from molecular clocks; see also Figure 1) and certain key steps, e.g., evolution of the structural protein collagen. This scheme takes the Fungi as the sister-group of Metazoa (e.g., Baldauf and Palmer, 1993), with a proposed divergence time of ca. 650 Myr. The Metazoa are divided into five superclades (sponges, diploblasts, ecdysozoans, lophotrochozoans, and deuterostomes), and this framework is based both on evidence from the fossil record and molecular biology. The Ediacaran faunas, of Vendian age (ca. 555–570 Myr), yield convincing sponges and cnidarians, best known from such animals as *Hydra* and the corals. Ediacaran cnidarians appear to belong to a group known as the anthozoans, which within the Cnidaria are probably the most primitive. Other cnidarians, and possibly the secondarily simplified placozoans and myxozoans (not shown), may have evolved later. All these groups are diploblastic (i.e., two germ layers giving rise respectively to ectoderm and endoderm). The other main group of diploblasts is the ctenophores (not shown), and these first appear in the Chengjiang fauna. A controversial and imperfectly defined group of Ediacaran organisms are referred to as the Vendobionta. They may represent very primitive Metazoa, becoming extinct in the earliest Cambrian. Ediacaran faunas may also house representatives of the stem-groups of at least two of the triploblast (i.e., three germ layers, with addition of mesoderm) superclades, but their principal evolutionary radiations were in the Cambrian. Ecdysozoans (which moult or ecdyse an exoskeleton) include various worms (nematodes, e.g., *C. elegans*, priapulids) and arthropods, the latter including the more primitive lobopodians and anomalocaridids. Lophotrochozoans, another neologism referring to a feeding apparatus (lophophore) and type of larva (trochophore), include many worms (annelids, nemerteans, and the platyhelminths of which the acoels may be the most primitive), as well as brachiopods, molluscs (including the bizarre xenoturbellids), and extinct halkieriids. Both ecdysozoans and lophotrochozoans are protostomes; that is, the embryological blastopore formed by the process of gastrulation gives rise to the mouth. The final superclade has an embryology whereby the mouth is formed secondarily, hence the name deuterostomes. This superclade comprises the hemichordates, echinoderms, e.g., sea urchin, and chordates, e.g., zebrafish, frog, and mouse.

deep past is legitimate, especially when the correlation is extended for two or three times beyond any known data point. Microevolutionary processes whereby, for example, catastrophic reduction of a population size (population bottleneck) or fortuitous colonization by a tiny cohort beyond the normal range of a species (founder effect), can result in subsequent and very rapid evolutionary rebound. During such time, arguably rates of substitution will be dramatically altered as the molecular clock runs fast. Omland (1997) has invoked just such arguments to explain a positive correlation between morphological and molecular divergence observed in a number of disparate groups.

Despite all these caveats, there is a vigorous industry trying either to reconcile the known fossil record with estimates derived from molecular clocks, or alternatively, to dismiss the fossil record as a credible source of information. At present there is particular focus on three areas: Mesozoic mammals and birds, ancient prokaryotes, and Precambrian metazoans (Figure 1). Each case provides an interesting object lesson. Molecular clocks indicate strongly that modern groups of mammals and birds originated in the mid-Mesozoic and thus substantially earlier than any available fossils (e.g., Cooper and Penny, 1997; Kumar and Hedges, 1998). The latter first occurs in abundance in the early Tertiary, when it has been generally assumed that they were rapidly refilling the vacancies provided by the end-Cretaceous (K/T) mass extinction (Figure 1). In the case of the birds, Bleiweiss (1998) has shown that the Tertiary fossil record allows probabilistic estimates of the likelihood of discovering hitherto overlooked Mesozoic representatives of four major modern groups. He concludes the existing fossil record is indeed robust. Using a somewhat different approach, Foote et al. (1999; see also Benton, 1999) have also shown that the fossil record of mammals would have had to have undergone an order-of-magnitude decline in quality to explain the absence of the appropriate fossils in the Mesozoic (see also Flynn et al., 1999). It seems more credible that the explosive diversification of eutherian mammals, and also birds, in the early Tertiary (ca. 64–55 Myr) was a real event, with the molecular clock showing a corresponding acceleration (see Gingerich, 1986).

A reverse case, in which molecular clocks indicate a substantially younger origination time than the fossil record, has also led to an interesting denouement. On the basis of multiple protein clocks, R. F. Doolittle and coworkers (see Feng et al., 1997) markedly rescaled the estimated times of microbial origination. They proposed that the cyanobacteria, the one prokaryotic group to have a reasonable Precambrian history, originated substantially later than the fossil record had traditionally been taken to indicate (Figure 1). Given the general absence of diagnostic features in fossil cyanobacteria (but see Golubic et al., 1995), it seemed possible that the more ancient microbial remains could have belonged to other, perhaps long-extinct, groups of prokaryotes. The recovery, however, of cyanobacterial biomarkers (i.e., organic chemicals recovered from ancient sediments that are diagnostic of particular groups) from 2,700-Myr-old sediments (Brocks et al., 1999) suggests that it is the molecular estimates that are unreliable. This is most likely to have arisen because of extensive lateral transfer of genetic material, whereby genes are transferred, by agents such as viral vectors, between different species (Martin, 1996; see also Doolittle, 1999a, 1999b).

These examples suggest that the use of molecular clocks in establishing divergence times of major groups requires caution. Nevertheless, there is also considerable interest in the Cambrian "explosion." This is a key step in evolutionary history, representing a major diversification of animals with the establishment of various bodyplans and a concomitantly sophisticated ecology. The "explosion" is most obvious from the geologically abrupt appearance of shells and other hard parts, but is also recorded by locomotory activities imprinted in the seafloor (trace fossils), and soft-bodied preservation in Burgess Shale–type faunas (Conway Morris, 1998b). Once again, however, there is a substantial discrepancy between the fossil record and molecular clocks, with the latter (e.g., Bromham et al., 1998) indicating times of origination at least 500 Myr before the first animal fossils (Figure 1). This in turn has led to the invocation of a protracted interval of cryptic evolution, involving minute animals too small either to be readily fossilized or even to leave burrows suitable for preservation as trace fossils. An ancient origin for the animals, if accepted, would have considerable implications both for the history of life and molecular evolution. It could effectively reduce the Cambrian "explosion" to an evolutionary artefact, simply reflecting a scaling up of body sizes with animals large enough to fossilize, especially if equipped with a skeleton, and to produce trace fossils.

The wider context of this event, and the various difficulties in invoking a cryptic metazoan history prior to the Cambrian, have been commented upon elsewhere (Conway Morris, 1998c, 1998d; Valentine et al., 1999). Here I wish to address the important question of whether the ancestral metazoan was comparable to a ciliated larva, similar to that found in such groups as the annelids and molluscs and known as the trochophore. Such larvae today feed in the plankton and thus are known as planktotrophs. Although this concept has a respectable pedigree, it has been given a new lease on life by Davidson and coworkers (e.g., Peterson et al., 1997; Davidson and Ruvkun, 1999). They draw attention to the so-called "set-aside" cells, which are not directly involved with larval activities, but go to provide the future rudiment of the adult anatomy, with the remainder of the ciliated larva being either discarded or consumed during the catastrophic metamorphosis that is characteristic of the biphasic metazoan life cycle (i.e., indirect development with an alternation between a floating microscopic ciliated larvae and a macroscopic adult that usually inhabits the seafloor). The hypothesis put forward by Davidson is not without difficulties. These center on several problems, including the covariance between type of larvae and adult body size (planktotrophs usually develop into adults large enough to make trace fossils, for which there is no evidence in the earlier Proterozoic, Figure 1), phylogenetic speculation that contrary to received wisdom, animal groups with planktotrophic larvae are not primitive, and evidence for direct development from Cambrian embryos (see Conway Morris, 1998c, 1998e). Even so, alternative explanations are possible. Davidson's expectation that similar gene networks exist in the larvae of otherwise widely different metazoan groups

might yet be confounded by convergence (Holland and Holland, 1999, p. 637). Another important component of the argument by Davidson and others (Davidson and Ruvkun, 1999) is that the planktotrophic larvae of at least the sea urchins (echinoids) show restricted *Hox* activity (at present two genes only) in comparison with the battery of genes expressed in the adult. They see this as consistent with a limited number of *Hox* genes having a primitive function in larvae, which was taken over and elaborated into a full-fledged *Hox* cluster with the invention of the "set-aside" cells from which the complex adult emerged. This could well be the case, but it seems equally parsimonious to suggest that these *Hox* genes have been coopted for larval use, as may be the case with other genes such as *Brachyury* (see Peterson et al., 1999).

The distribution of *Hox* genes might provide other insights into the dramatic radiation of metazoans close to the Precambrian-Cambrian boundary (Figure 2). In particular, Adoutte et al. (1999) have suggested that the common possession of the *Hox* cluster in the three great branches of the more advanced animals with generally bilateral symmetry (hence Bilateria) (referred to as the deuterostomes, ecdysozoans, and lophotrochozoans; see Figure 2) indicates that their parallel and synchronous evolutionary radiations are best explained as a result of an external stimulus. Animal evolution, of course, did not start with the Cambrian "explosion." What can we discern prior to this event? The apparent prevalence of the more primitive diploblastic metazoans in the preceding Ediacaran age assemblages (Figure 2) would be consistent with a stage in genomic evolution exhibiting a less complex *Hox* assemblage. With some justification, Ediacaran fossils have become notorious as evolutionary enigmas, and even to the trained eye many look strange, if not bizarre. Bringing them into the fold of the new framework of metazoan phylogeny (Figure 2) suggests, however, that some of the more far-flung proposals can be reined in. Even so, some types, referred to as the Vendobionta, remain decidedly enigmatic. Perhaps they should be excluded altogether from the Metazoa, but conceivably they represent a side branch of the earliest metazoans equipped with an even simpler *Hox* component (Figure 2).

Macroevolution: What Hope for Neo-Darwinism?

The implications of the revolution in molecular biology and developmental processes for evolution are universally appreciated. For the most part, however, the new field of molecular evolution has paid rather less attention to the classic formulations of mechanisms that have largely revolved around the precepts of neo-Darwinism (but see Wallace, 1999). There have, of course, been dissenting voices, arguing for a plethora of processes in addition to neo-Darwinian mechanisms. These include species selection and the importance of contingent events, notably mass extinctions. Some of these arguments are laced with a rhetorical exegesis, and notably have paid little attention to molecular insights. Effecting an evolutionary synthesis of the disparate strands will not be easy, but here I wish to draw attention briefly to several themes. The dramatic effects of ectopic expression of genes such as *Pax-6*, combined with the apparent ease of radical reconfigurations of body architecture by misexpression of homeotic genes, especially in the arthropods, would seem to open a rich field of macroevolutionary possibilities. This, in turn, invites renewed interest in earlier speculations on saltatory modes of evolution, sometimes encapsulated in the concept of "hopeful monsters," championed by such individuals as Richard Goldschmidt and Otto Schindewolf. Among molecular biologists, interest in such a program has been muted. There are, however, some exceptions, such as the overview offered by Schwartz (1999), which proposes that macroevolutionary jumps should be placed in the context of both developmental genetics and the supposed absence of intermediates connecting body-plans from the fossil record. Schwartz's views can be summarized by a brief quotation from his book *Sudden Origins* (p. 369), in which his thesis "demonstrates how a mutation involving the expression of homeobox genes can produce a morphological, physiological, or behavioral novelty that would emerge in a full blown and viable state." Continuing along this macroevolutionary theme, he then writes: "There would not have been a string of graded morphological intermediates, . . . [so] we can appreciate why 'missing links' are so elusive in the fossil record. They probably did not exist." This seems, however, to be a misreading of the available evidence. Homeotic and other developmental genes do not float in a kind of limbo ready for macroevolutionary adventures, but are intimately tied to complex gene networks that lead to the ordered end-product, such as the eye. In addition, the case of *Pax-6* is instructive both because of its multiple functions and the fact that groups such as nematodes possess this gene but lack eyes.

The continuing advances in developmental genetics will continue to excite the attention of macroevolutionists, although the lability of some homeobox genes possibly linked to sexual selection and hybrid sterility (e.g., Ting et al., 1998) is a reminder that some connections to microevolutionary processes and population genetics will turn out to be more fruitful than is perhaps generally recognized. As noted above, the discrepancies in divergence times that are evident from molecular clocks could become more tractable when placed in a context of population genetics and natural selection (see Gillespie, 1986). Cavalier-Smith et al. (1996, p. 2040), for example, list various scenarios involving mutation rates, selection pressure, and population bottlenecks that allow variation in the rates of molecular clocks to fit comfortably into a neo-Darwinian framework.

At the risk of oversimplification, it seems broadly correct to say that while most developmental biologists would concede the molecules they study are the product of selection, there is little interest in functional constraint and adaptation. Striking examples of molecular convergence, such as in fish antifreeze proteins (Chen et al., 1997), cytokinases (Beschin et al., 1999), and apolipoproteins (Lawn et al., 1997) tend to be greeted with surprise, yet these examples also suggest that adaptational constraints on molecular architecture may be more pervasive than is generally appreciated. Lee (1999) gives a short but telling review of evidence for adaptive shifts in molecular architecture. His principal concern is for the potential loss of a historical signal (see below), but we need to enquire not only what constraints of function might be imposed on particular molecules, but

even gene networks (see Nagy, 1998). Indeed, the "remarkable similarities" to animals that are seen in the dorsoventral patterning genes of plants (Sessions and Yanofsky, 1999) is a further reminder that adaptational constraints and convergences are widespread, if not ubiquitous.

New Phylogenies, New Problems

Phylogenies, especially those of the Metazoa, have been revolutionized by molecular data. Earlier surprises, such as the placement of the brachiopods (a phylum of bivalved marine animals) (Figure 2), long thought to lie close to the deuterostomes, within the protostomes have been codified to the extent that the triploblasts are now divided with some confidence into three superclades (the deuterostomes, ecdysozoans, and lophotrochozoans) (de Rosa et al., 1999; see also Figure 2). Relationships within these superclades, however, remain considerably more problematic, at least in terms of molecular data. In the lophotrochozoans, for example, the majority of the component phyla emerge as branches from a single point and so form an unresolved polychotomy, while in the ecdysozoans the previously unexpected link between nematodes and arthropods has not yet led to a more precisely resolved phylogeny. Nor, of course, are we any better informed as to how anything like a nematode could have evolved from any other group of ecdysozoan. More generally, despite successes in redefining the nature of the triploblastic phyla as a whole, metazoan phylogenies continue to show considerable instability, and the placement of key groups such as the calcareous sponges (unusual in secreting a massive skeleton of calcium carbonate), the sea-gooseberries or ctenophores, and simple placozoans (see Figure 2) are all subject to considerable variability. Moreover, Abouheif et al. (1998) have cast doubt on the utility of 18S rRNA, the molecule of choice in metazoan phylogeny, as well as using the molecular data to infer the Cambrian "explosion." The usual response is to turn to other molecules, such as elongation factor–1α (e.g., McHugh 1997), but even so it seems doubtful whether a uniquely satisfactory and coherent solution will emerge.

If matters are still unresolved in the Metazoa, then the situation among the prokaryotes is even more confused. In a sobering analysis, Teichmann and Mitchison (1999) identified extensive lateral gene transfer (see also Doolittle, 1999a, 1999b; Garcia-Vallvé et al., 1999) as largely compromising a phylogenetic analysis of the major groups of prokaryote. To be sure, the two prokaryote Kingdoms (Archea and Bacteria) retain their coherence, and for the most part, the phylogeny of closely related groups is also unproblematic. But the key question of the interrelationships of the major prokaryotic groups seems at present to be almost intractable. It now seems to be generally assumed that lateral gene transfer confounds prokaryotic phylogenies, but is a less serious problem when it comes to the eukaryotes. Instances of transfer, e.g., of group I introns, in the latter (e.g., Cho and Palmer, 1999) are a reminder that resolution of particular phylogenies might be less straightforward than imagined (see also Syvanen, 1994).

Conclusion

Molecular biology enlarges our horizons, but without a firm basis in evolutionary theory, the most interesting questions still elude us. There do, however, seem to be some trends. First, the diversity of life is, in molecular terms, little more than skin deep. Most, perhaps all, of the basic building blocks necessary for organismal complexity were available long before the emergence of multicellularity. How and when the gene networks and regulatory mechanisms that led to complex organs and functioning organisms were assembled is largely obscure. Cooption and transfer of function could be equally important, but here, too, we can do little more than articulate general principles. Just as the phenotypic diversity of life excites the imagination of a naturalist, so the range of molecules and the sophistication of their biochemistries impress the molecular biologist. In comparison, the underlying constraints on form and the inevitability of convergences have received far less emphasis. Why should this be so? There seem to be two reasons. The first is that if evolution is in some sense channeled, then this reopens the controversial prospect of a teleology; that is, the process is underpinned by a purpose. It is no coincidence that interest in the Anthropic Principle, which broadly seeks evidence for the boundary conditions of the Big Bang and the ensuing physics and chemistry uniquely favoring the emergence of life (Barrow and Tipler, 1986, see in particular chapter 8), is being extended to the fields of biochemistry and molecular biology (for one view, see Denton, 1998). Second, the study of evolution is strongly historical, and the prospect of a seemingly unique trajectory of circumstances for the history of life may be discouraging to those who are seeking general principles. Yet here, too, the search for convergences may yield unexpected insights, and the work by Travisano and coworkers on the replicability of evolution in bacteria (e.g., Travisano et al., 1995; Rainey and Travisano, 1998) is of particular importance.

I suspect that the topic of convergences will become an increasing focus of attention, and will be a key element in linking molecular and whole-organism biology. There are many potential examples, but I will mention only three. The first concerns behavior, which as with these (and any other) examples is underpinned by molecules. A key step in speciation, and potentially the initiation of an adaptive radiation, is the imposition of population bottlenecks and founder-flush events. This process of drastic reduction in population size followed by a rapid rebound, perhaps in a novel environment remote from the parent species, might be expected to favor a correspondingly wide repertoire of behavioral types. Yet in experiments that imposed a substantial disruption in genetic variance, the patterns of courtship in the housefly were actually strongly convergent and so overrode founder-flush events (Meffert et al., 1999). Nothing yet appears to be known of how the gene networks are modified during such events, but it is likely that their considerable variation has little effect on the behavioral end-result. So too with the sense of smell. In reviewing olfaction, Hildebrand and Shepherd (1997) noted that "a common set of neural mechanisms has evolved across phyla for detecting and discriminating among olfactory

stimuli." Although the odorant-binding proteins in arthropods and vertebrates are not the same, the basic structure of the receptors, notably the glomeruli, are remarkably similar. As Hildebrand and Shepherd (1997) note, antennae and noses work in basically the same way. A third striking example of convergence is between two unrelated fish, respectively from South America (*Eigenmannia*) and Africa (*Gymnarchus*), that produce an electric signal known as the jamming avoidance response, which acts to baffle a potential predator. As Kawasaki and coworkers (e.g., Kawasaki, 1996; Guo and Kawasaki, 1997) have shown, each fish (or its lineage) has evolved an identical algorithm for jamming, but quite independently. In each case the underlying basis may derive from the ability to echo-locate, but the crucial point is that the area of brain responsible for this signal production is different in either fish. Remarkably similar end-points can be arrived at from quite different starting points.

It seems that these examples expose a basic tension in the study of evolution. The question we need to ask is whether a structure (molecular or organismal) is similar because it shares a common ancestry and thus is homologous or because there is no (or very few) alternative. The former approach, of course, underpins most evolutionary thinking and has potentially a strong historical component. Convergence, on the other hand, points toward adaptive constraint in which the historical dimension is relatively unimportant. In looking to the future, paradoxically we also look to the past. Our present dilemma echoes to some extent two strands of Greek philosophy, the world of flux and continuous change discussed by Heraclitus versus the more famous concept of eternal forms adumbrated by Plato. Evolution obviously occurs in the river of time, and in many ways the world of the Cambrian, let alone the Archaean, is very different from that of today. Yet, as discussed earlier, the very similar genetic architecture that underpins the arm with which I write this article and the wing of the passing fly introduces the sobering possibility that much of organismal architecture is dependent on a set of "toolboxes," each opened as and when the need arises. And this is perhaps the central conundrum of evolution: how do we balance the process of change against the emergence of form?

Acknowledgments

Two anonymous referees provided very helpful critiques. I also thank Sandra Last for typing numerous versions of this manuscript and Sharon Capon for drafting figures. My work is supported by the Leverhulme Trust, Natural Environment Research Council, and St. John's College, Cambridge. Cambridge Earth Sciences Publication 5785.

References

Abouheif, E., Zardoya, R., and Meyer, A. (1998). Limitations of metazoan 18S rRNA sequence data: implications for reconstructing a phylogeny of the animal kingdom and inferring the reality of the Cambrian explosion. J. Mol. Evol. *47*, 394–405.

Adoutte, A., Balavoine, G., Lartillot, N., and de Rosa, R. (1999). Animal evolution—the end of the intermediate taxa? Trends Genet. *15*, 104–108.

Arendt, D., and Nübler-Jung, K. (1999). Comparison of early nerve cord development in insects and vertebrates. Development *126*, 2309–2325.

Balavoine, G. (1998). Are platyhelminthes coelomates without a coelom? An argument based on the evolution of *Hox* genes. Amer. Zool. *38*, 843–858.

Baldauf, S.L., and Palmer, J.D. (1993). Animal and fungi are each other's closest relatives: congruent evidence from multiple proteins. Proc. Natl. Acad. Sci. USA *90*, 11558–11562.

Barrow, J.D., and Tipler, F.J. (1986). The Anthropic Cosmological Principle (Oxford: Oxford University Press).

Benton, M.J. (1999). Early origins of modern birds and mammals: molecules vs. morphology. BioEssays *21*, 1052–1058.

Beschin, A., Bilej, M., Brys, L., Torreele, E., Lucas, R., Magez, S., and De Baetselier, P. (1999). Convergent evolution of cytokines. Nature *400*, 627–628.

Britten, R.J. (1986). Rates of DNA sequence evolution differ between taxonomic groups. Science *231*, 1393–1398.

Brocks, J.J., Logan, G.A., Buick, R., and Summons, R.E. (1999). Archean molecular fossils and the early rise of eukaryotes. Science *285*, 1033–1036.

Bromham, L., Rambaut, A., Fortey, R., Cooper, A., and Penny, D. (1998). Testing the Cambrian explosion hypothesis by using a molecular dating technique. Proc. Natl. Acad. Sci. USA *95*, 12386–12389.

Cavalier-Smith, T., Allsopp, M.T.E.P., Chao, E.E., Boury-Esnault, N., and Vacelet, J. (1996). Sponge phylogeny, animal monophyly, and the origin of the nervous system: 18S rRNA evidence. Can. J. Zool. *74*, 2031–2045.

Chen, L., DeVries, A.L., and Cheng, C.-H. (1997). Convergent evolution of antifreeze glycoproteins in Antarctic notothenioid fish and Arctic cod. Proc. Natl. Acad. Sci. USA *94*, 3817–3822.

Chiu, J., De Salle, R., Lam, H.-M., Meisel, L., and Coruzzi, G. (1999). Molecular evolution of glutamate receptors: a primitive signaling mechanism that existed before plants and animals diverged. Mol. Biol. Evol. *16*, 826–838.

Cho, Y., and Palmer, J.D. (1999). Multiple acquisitions via horizontal transfer of a Group 1 intron in the mitochondrial *cox1* gene during evolution of the Araceae family. Mol. Biol. Evol. *16*, 1155–1165.

Collins, A.G. (1998). Evaluating multiple alternative hypotheses for the origin of Bilateria: an analysis of 18S rRNA molecular evidence. Proc. Natl. Acad. Sci. USA *95*, 15458–15463.

Conway Morris, S. (1998a). The evolution of diversity in ancient ecosystems: a review. Philos. Trans. R. Soc. Lond. B. Biol. Sci. *353*, 327–345.

Conway Morris, S. (1998b). The Crucible of Creation: The Burgess Shale and the Rise of Animals (Oxford: Oxford University Press).

Conway Morris, S. (1998c). Early metazoan evolution: reconciling paleontology and molecular biology. Amer. Zool. *38*, 867–877.

Conway Morris, S. (1998d). Metazoan phylogenies: falling into place or falling to pieces? A palaeontological perspective. Curr. Opin. Genet. Dev. *8*, 662–667.

Conway Morris, S. (1998e). Eggs and embryos from the Cambrian. BioEssays *20*, 676–682.

Cooper, A., and Penny, D. (1997). Mass survival of birds across the Cretaceous-Tertiary boundary: molecular evidence. Science *275*, 1109–1113.

Davidson, E.H., and Ruvkun, G. (1999). Themes from a NASA workshop on gene regulatory processes in development and evolution. J. Exp. Zool. (Mol. Dev. Evol.) *285*, 104–115.

Denton, M.J. (1998). Nature's Destiny: How the Laws of Biology Reveal Purpose in the Universe. (New York: Free Press).

De Robertis, E.M., and Sasai, Y. (1996). A common plan for dorsoventral patterning in Bilateria. Nature *380*, 37–40.

de Rosa, R., Grenier, J.K., Andreeva, T., Cook, C.E., Adoutte, A., Akam, M., Carroll, S.B., and Balavoine, G. (1999). Hox genes in brachiopods and priapulids and protostome evolution. Nature *399*, 772–776.

Donovan, S.K., and Paul, C.R.C., eds. (1998). The Adequacy of the Fossil Record (Chichester: Wiley).

Doolittle, W.F. (1999a). Phylogenetic classification and the universal tree. Science *284*, 2124–2128.

Doolittle, W.F. (1999b). Lateral genomics. Trends Biochem. Sci. *9* (12), M5-M8.

Eizinger, A., and Sommer, R.J. (1997). The homeotic gene *lin-39* and the evolution of nematode epidermal cell fates. Science *278*, 452–455.

Eizinger, A., Jungblut, B., and Sommer, R.J. (1999). Evolutionary change in the functional specificity of genes. Trends Genet. *15*, 197–202.

Feng, D.-F., Cho, G., and Doolittle, R.F. (1997). Determining divergence times with a protein clock: update and reevaluation. Proc. Natl. Acad. Sci. USA *94*, 13028–13033.

Finkelstein, R., and Boncinelli, E. (1994). From fly head to mammalian forebrain: the story of *otd* and *otx*. Trends Genet. *10*, 310–315.

Flynn, J.J., Parrish, J.M., Rakotosamimana, B., Simpson, W.F., and Wyss, A.R. (1999). A Middle Jurassic mammal from Madagascar. Nature *401*, 57–60.

Foote, M., Hunter, J.P., Janis, C.M., and Sepkoski, J.J. (1999). Evolutionary and preservational constraints on origins of biologic groups: divergence times of eutherian mammals. Science *283*, 1310–1314.

Garcia-Vallvé, S., Palau, J., and Romeu, A. (1999). Horizontal gene transfer in glycosyl hydrolases inferred from codon usage in *Escherichia coli* and *Bacillus subtilis*. Mol. Biol. Evol. *16*, 1125–1134.

Gillespie, J.H. (1986). Natural selection and the molecular clock. Mol. Biol. Evol. *3*, 138–158.

Gingerich, P.D. (1986). Temporal scaling of molecular evolution in primates and other mammals. Mol. Biol. Evol. *3*, 205–221.

Golubic, S., Sergeev, V.N., and Knoll, A.H. (1995). Mesoproterozoic *Archaeoellipsoides*: akinetes of heterocystous cyanobacteria. Lethaia *28*, 285–298.

Guo, Y.-X., and Kawasaki, M. (1997). Representation of accurate temporal information in the electrosensory system of the African electric fish, *Gymnarchus niloticus*. J. Neurosci. *17*, 1761–1768.

Hanelt, B., van Schyndel, D., Adema, C.M., Lewis, L.A., and Loker, E.S. (1996). The phylogenetic position of *Rhopalura ophiocomae* (Orthonectida) based on 18S ribosomal DNA sequence analysis. Mol. Biol. Evol. *13*, 1187–1191.

Hildebrand, J.G., and Shepherd, G.M. (1997). Mechanisms of olfactory discrimination: converging evidence for common principles across phyla. Ann. Dev. Neurosci. *20*, 595–631.

Holland, N.D., and Holland, L.S. (1999). Amphioxus and the utility of molecular genetic data for hypothesizing body part homologies between distantly related animals. Amer. Zool. *39*, 630–640.

Hoshiyama, D., Suga, H., Iwabe, N., Koyanagi, M., Nikoh, N., Kuma, K.-i, Matsuda, F., Honjo, T., and Miyata, T. (1998). Sponge *Pax* cDNA related to *Pax-2/5/8* and ancient duplications in the *Pax* family. J. Mol. Evol. *47*, 640–648.

Kawasaki, M. (1996). Comparative analysis of the jamming avoidance response in African and South American wave-type electric fishes. Biol. Bull. *191*, 103–108.

Kobayashi, M., Furuya, H., and Holland, P.W.H. (1999). Dicyemids are higher animals. Nature *401*, 762.

Kumar, S., and Hedges, S.B. (1998). A molecular timescale for vertebrate evolution. Nature *392*, 917–920.

Kupfermann, H., Salta, Y., Takahata, N., Tichy, H., and Klein, J. (1999). Evolution of *Mhc-DRB* introns: implications for the origin of primates. J. Mol. Evol. *48*, 663–674.

Lacalli, T.C. (1996). Frontal eye circuitry, rostral sensory pathways and brain organization in amphioxus larvae: evidence from 3D reconstructions. Philos. Trans. R. Soc. Lond. B. Biol. Sci. *351*, 243–263.

Lacalli, T.C., Gilmour, T.H.J., and Kelly, S.J. (1999). The oral nerve plexus in amphioxus larvae: function, cell types and phylogenetic significance. Proc. R. Soc. Lond. B. Biol. Sci. *266*, 1461–1470.

Lawn, R.M., Schwartz, K., and Patthy, L. (1997). Convergent evolution of apolipoprotein(a) in primates and hedgehog. Proc. Natl. Acad. Sci. USA *94*, 11992–11997.

Lee, M.S.Y. (1999). Molecular phylogenies become functional. Trends Ecol. Evol. *14*, 177–178.

Leys, S.P., Mackie, G.O., and Meech, R.W. (1999). Impulse conduction in a sponge. J. Exp. Biol. *202*, 1139–1150.

Lynch, M. (1999). The age and relationships of the major animal phyla. Evolution *53*, 319–325.

McHugh, D. (1997). Molecular evidence that echiurans and pogonophorans are derived annelids. Proc. Natl. Acad. Sci. USA *94*, 8006–8009.

Martin, W.F. (1996). Is something wrong with the tree of life? BioEssays *18*, 523–527.

Meffert, L.M., Regan, J.L., and Brown, B.W. (1999). Convergent evolution of the mating behaviour of founder-flush populations of the housefly. J. Evol. Biol. *12*, 859–868.

Mokady, O., Dick, M.H., Lackschewitz, D., Schierwater, B., and Buss, L.W. (1998). Over one-half billion years of head conservation? Expression of an ems class gene in *Hydractinia symbiolongicarpus* (Cnidaria: Hydrozoa). Proc. Natl. Acad. Sci. USA *95*, 3673–3678.

Müller, W.E.G., Kruse, M., Koziol, C., Müller, J.M., and Leys, S.P. (1998). Evolution of early Metazoa: phylogenetic status of the Hexactinellida within the phylum Porifera. In Molecular Evolution: Towards the Origin of Metazoa, W.E.G. Müller, ed. (Berlin: Springer), pp. 141–156.

Nagy, L. (1998). Changing patterns of gene regulation in the evolution of arthropod morphology. Amer. Zool. *38*, 818–828.

Noren, M., and Jondelius, U. (1997). *Xenoturbella*'s molluscan relatives. . . . Nature *390*, 31–32.

Omland, K.E. (1997). Correlated rates of molecular and morphological evolution. Evolution *51*, 1381–1393.

Ono, K., Suga, H., Iwabe, N., Kuma, K.-i, and Miyata, T. (1999). Multiple protein-tyrosine phosphatases in sponges and explosive gene duplication in the early evolution of animals before the parazoan-eumetazoan split. J. Mol. Evol. *48*, 654–662.

Perovic, S., Krasko, A., Prokic, I., Müller, I.M., and Müller, W.E.G. (1999). Origin of neuronal-like receptors in Metazoa: cloning of a metabotrophic glutamate/GABA-like receptor from the marine sponge *Geodia cydonium*. Cell Tissue Res. *296*, 395–404.

Peterson, K.J., Cameron, R.A., and Davidson, E.H. (1997). Set-aside cells in a maximal indirect development: evolutionary and developmental significance. BioEssays *19*, 623–631.

Peterson, K.J., Cameron, R.A., Tagawa, K., Satoh, N., and Davidson, E.H. (1999). A comparative molecular approach to mesodermal patterning in basal deuterostomes: the expression pattern of *Brachyury* in the enteropneust hemichordate *Ptychodera flava*. Development *126*, 85–95.

Rainey, P.B., and Travisano, M. (1998). Adaptive radiation in a heterogeneous environment. Nature *394*, 69–72.

Reuter, M., Raikova, O.I., and Gustafsson, M.K.S. (1998). An endocrine brain? The pattern of FMRF-amide immunoreactivity in Acoela (Plathelminthes), Tissue Cell *30*, 57–63.

Ruiz-Trillo, I., Riutort, M., Littlewood, D.T.J., Herniou, E.A., and Baguna, J. (1999). Acoel flatworms: earliest extant bilaterian metazoans, not members of platyhelminthes. Science *283*, 1919–1923.

Schäcke, H., Rinkevich, B., Gamulin, V., Müller, I.M., and Müller, W.E.G. (1994). Immunoglobin-like domain is present in the extracellular part of the receptor tyrosine kinase from the marine sponge *Geodia cydonium*. J. Mol. Recog. *7*, 273–276.

Schierwater, B., and Kuhn, K. (1998). Homology of *Hox* genes and the zootype concept in early metazoan evolution. Mol. Phylogenet. Evol. *9*, 375–381.

Schwartz, J.H. (1999). Sudden Origins: Fossils, Genes, and the Emergence of Species (New York: Wiley).

Sessions, A., and Yanofsky, M.F. (1999). Dorsoventral patterning in plants. Genes Dev. *13*, 1051–1054.

Siddall, M.E., Martin, D.S., Bridge, D., Desser, S.S., and Cone, D.K. (1995). The demise of a phylum of protists: phylogeny of Myxozoa and other parasitic Cnidaria. J. Parasitol. *81*, 961–967.

Smith, K.M., Gee, L., Blitz, I.L., and Bode, H.R. (1999). *CnOtx*, a member of the *Otx* gene family has a role in cell movement in hydra. Dev. Biol. *212*, 392–404.

Syvanen, M. (1994). Horizontal gene transfer: evidence and possible consequences. Annu. Rev. Genet. *28*, 237–261.

Teichmann, S.A., and Mitchison, G. (1999). Is there a phylogenetic signal in prokaryotic proteins? J. Mol. Evol. *49*, 98–107.

Ting, C.T., Tsaur, S.C., Wu, M.-L., and Wu, C.-I. (1998). A rapidly evolving homeobox at the site of a hybrid sterility gene. Science *282*, 1501–1504.

Travisano, M., Mongold, J.A., Bennett, A.F., and Lenski, R.E. (1995). Experimental tests of the roles of adaptation, chance, and history in evolution. Science *267*, 87–90.

Umesono, Y., Watanabe, K., and Agata, K. (1999). Distinct structural domains in the planarian brain defined by the expression of evolutionarily conserved homeobox genes. Dev. Genes Evol. *209*, 31–39.

Vacelet, J., and Boury-Esnault, N. (1995). Carnivorous sponges. Nature *373*, 333–335.

Valentine, J.W., Jablonski, D., and Erwin, D.H. (1999). Fossils, molecules and embryos: new perspectives on the Cambrian explosion. Development *126*, 851–859.

Wallace, A. (1999). Variable segment number in centipedes: population genetics meets evolutionary developmental biology. Evol. Dev. *1*, 62–69.

Williams, N.A., and Holland, P.W.H. (1998). Gene and domain duplication in the chordate *Otx* gene family: insights from Amphioxus *Otx*. Mol. Biol. Evol. *15*, 600–607.

Wistow, G. (1993). Lens crystallins: gene recruitment and evolutionary dynamism. Trends Biochem. Sci. *18*, 301–306.

Wray, G.A. (1999). Evolutionary dissociations between homologous genes and homologous structures. In Homology. G.R. Bock and G. Cardew, eds. (Chichester: Wiley), Novartis Foundation Symposium *222*, pp. 189–203.

Wu, L.H., and Lengyel, J.A. (1998). Role of caudal in hindgut specification and gastrulation suggest homology between *Drosophila* amnioproctodeal invagination and vertebrate blastopore. Development *125*, 2433–2442.